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# (54) THIAZOLE AND IMIDAZO[4,5-B]PYRIDINE COMPOUNDS AND THEIR PHARMACEUTICAL USE

THIAZOL UND IMIDAZO[4,5-B]PYRIDIN VERBINDUNGEN UND IHRE VERWENDUNG ALS PHARMAZEUTIKA

COMPOSES THIAZOLE ET IMIDAZO [4,5-B] PYRIDINE ET LEUR UTILISATION PHARMACEUTIQUE

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(73) Proprietors:
- **Novartis AG**
**4056 Basel (CH)**
Designated Contracting States:
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- **Novartis Pharma GmbH**
**1230 Wien (AT)**
Designated Contracting States:
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(72) Inventor: **Révész, László**
**CH-4106 Therwil (CH)**

(74) Representative: **de Weerd, Petrus G.W. et al**
**Novartis International AG**
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**4002 Basel (CH)**

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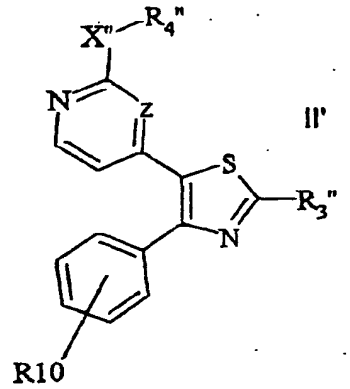
EP 1 224 185 B1

## Description

**[0001]** This invention relates to heterocyclic compounds, in particular to thiazoles and imidazopyridines and to their use for treating TNFα and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e. g. osteoporosis.

**[0002]** Accordingly the present invention provides a compound of formula II'




II'

wherein

$R_4$" is phenyl or $C_3$-$C_7$cycloalkyl each of which is optionally mono-substituted by halogen, $C_1$-$C_4$alkyl $C_1$-$C_4$alkoxy, hydroxy, trihalomethyl or optionally mono-or di-$C_1$-$C_4$alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N; $R_{10}$ is halogen;

$R_3$" is H, $C_1$-$C_4$alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di-$C_{1-4}$alkyl substituted amino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from $C_1$-$C_4$alkyl; halogen, hydroxy, $C_1$-$C_4$alkoxy, or optionally mono-or di-$C_1$-$C_4$alkyl substituted amino; Z is N or CH and

X" is -NH-Y'-, -O- or -S-, where Y' is $-CH_2-$, $-CH_2-CH_2$, $-CH(CH_3)-$ or a direct bond,

and prodrug ester derivatives thereof which are convertible by solvolysis or cleavage under physiological conditions to the compound of formula II' comprising the free hydroxyl group; and acid addition salts thereof.

**[0003]** Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F.

**[0004]** Above and elsewhere in the present description the terms such as "$C_{3-18}$heteroaryl, $C_{4-19}$ heteroaralkyl and $C_{3-18}$heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g. N, O or S, and which in the case of $C_{4-19}$ heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom.

Preferably $R_4$" is unsubstituted or monosubstituted by halogen, $C_{1-4}$alkyl (e.g. methyl), $C_{1-4}$alkoxy (e.g. methoxy), hydroxy or $CF_3$.

**[0005]** Preferably $R_{10}$ is halogen, e.g. F.

**[0006]** Preferably X' is -NH-Y' where Y' is $-CH(CH_3)-$.

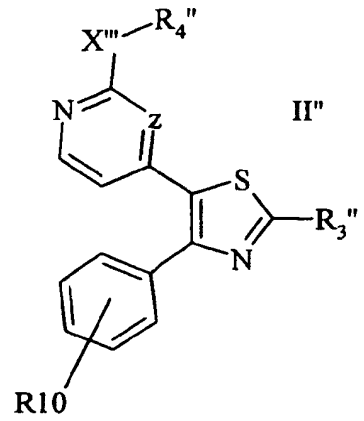
**[0007]** The Invention includes the following compounds:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methyl-piperidine-1-yl)thiazole;
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-NH-piperidine-1-yl)thiazole;
4-(4-Fluorophenyl)2-(4-methylpiperidine-1-yl)5-(2-[cyclopropyl-methyl]amino-4-pyridinyl)thiazole and
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole;

**[0008]** The novel thiazoles of the invention, in particular the compounds of formula II' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

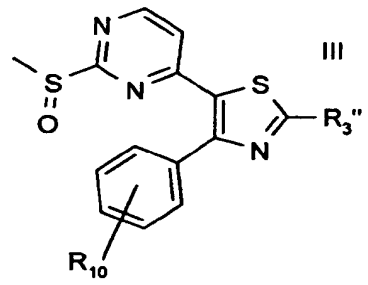
Agents of the Invention of formula II"

**[0009]**

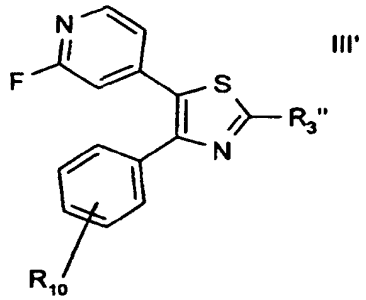



II"

wherein $R_3$", $R_5$", $R_{10}$ and Z are as previously defined and X" is -NH-, may be prepared by reacting the corresponding precursor compound of formula III or III'



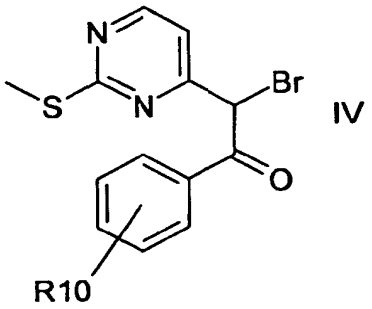

III



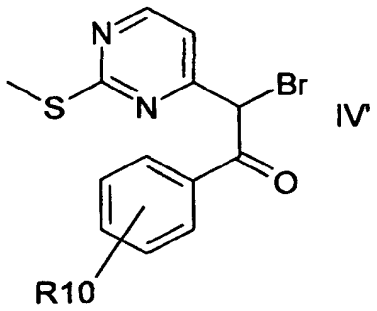

III'

wherein $R_3$" and $R_{10}$ are as previously defined, with the corresponding $R_4$"-$NH_2$ derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane. Thereafter, if desired, the compound of Formula I" obtained may be converted into a further compound of Formula I" or otherwise treated as required.

**[0010]** The precursor compound of formula III may be prepared by controlled oxidation of the corresponding 5 (2-methylthio-4-pyrimidinyl)-4-phenythiazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(4-pyrimidinyl/pyridinyl) 4-phenylthiazole compound may be prepared by contacting the corresponding acetophenone precursor compound of formula IV or IV'



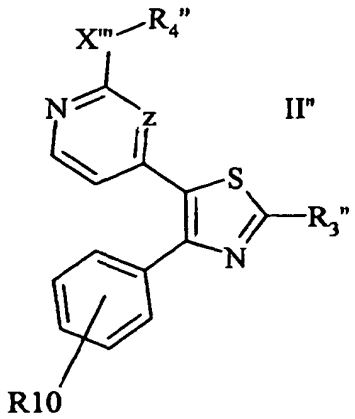
IV



IV'

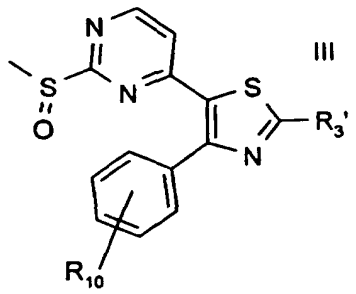
wherein $R_{10}$ is as defined above, with a corresponding thioamide of formula $R_3'C(S)NH_2$, typically at elevated temperature. The compounds of formula IV and IV' may be prepared by bromination of the corresponding acetophenone, e. g. 2-(2-methylthio-4-pyrimidinyl)acetophenone. The acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with the corresponding pyrimidine, e.g. 4-methyl-2-(methylthio) pyrimidine, for instance in a THF containing organic solvent with cooling.

**[0011]** Thus in a further aspect the invention includes a process for the preparation of a compound of formula II"

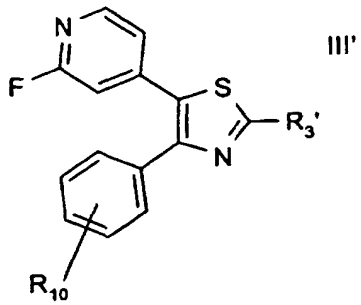


II"

wherein $R_3$", $R_4$", $R_{10}$ and Z are as previously defined and X" is -NH-, which comprises reacting the corresponding precursor compound of formula III or III'



III



III'

wherein $R_3$" and $R_{10}$ are as previously defined, with the corresponding $R_4$"-$NH_2$ amine, and thereafter, if desired, converting the compound of formula II" obtained into a further compound of formula II" or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

**[0012]** It will be appreciated that certain Agents of the Invention may contain at least 1 assymetric carbon atom; for instance when Y is substituted alkylene, e.g. when Y" is -$CH(CH_3)$- for the compounds of formula II' above. The resulting

diastereomers and enantiomers are encompassed by the instant invention. Preferably, however, e.g. for pharmaceutical use in accordance with the invention, the compounds of formulae I, are provided in pure or substantially pure epimeric form, e.g. as compositions in which the compounds are present in a form comprising at least 90%, e.g. preferably at least 95% of a single epimer (i.e. comprising less than 10%, e.g. preferably less than 5% of other epimeric forms). Preferred epimeric compounds of formula I are described hereinafter in the Examples.

**[0013]** The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

**[0014]** Agents of the Invention may also exist in the form of pharmaceutically acceptable salts, and as such are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

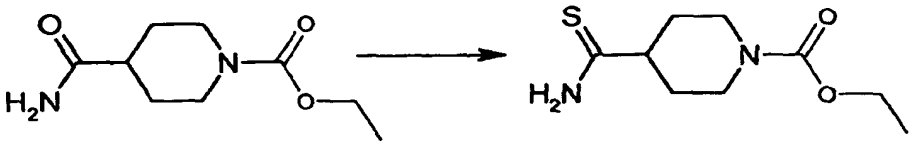
**[0015]** The synthesis of Agents of the Invention is further described in the following Examples.

## EXAMPLES

### Example 1 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

#### a) N-Ethoxycarbonylpiperidine-4-thiocarboxamide

**[0016]**



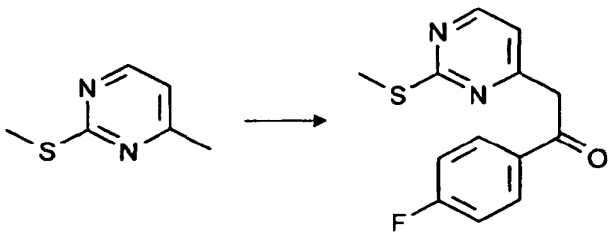
N-Ethoxycarbonylpiperidine-4-carboxamide (6g 30mmol) in toluene (300ml) is treated with Lawesson's reagent (6.1g 15mmol) at room teperature for 18h. The reaction mixture is evaporated and purified by $SiO_2$ chromatography (acetone/cyclohexane 20/80) to yield the title compound, which is recrystallised from hexanes (3.6g 52.5%)

1H-NMR (400MHz; $CDCl_3$): 1.28 (t, 3H); 1.72-1.83 (dq, 2H); 1.95 (d, 2H); 2.68-2.88 (m, 3H); 4.18 (q, 2H); 4.30 (bs, 2H); 6.92 (bs, 1H, NH); 7.51 (bs, 1H, NH)

MS (m/z) CI: 217 (MH+, 50); 171 (100).

**b) 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone**

**[0017]**

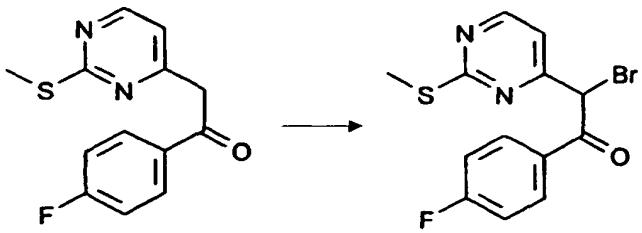


n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78 C. 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over $Na_2SO_4$ and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/ hexane.

1H-NMR (200 MHz $CDCl_3$): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, l H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomery, signals may be duplicated.

**c) 4-Fluoro-2-bromo -2-(2-methylthio-4-pyrimidinyl)acetophenone**

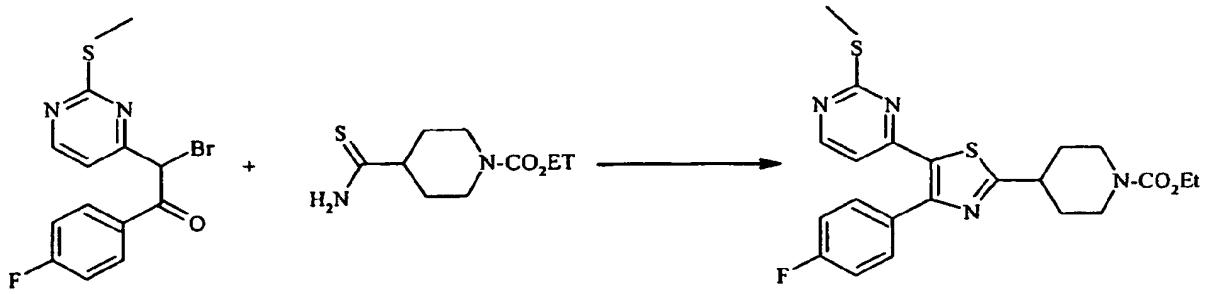
**[0018]**



Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The residue is taken up in a saturated solution of $NaHCO_3$ and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over $Na_2SO_4$ and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

d) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole

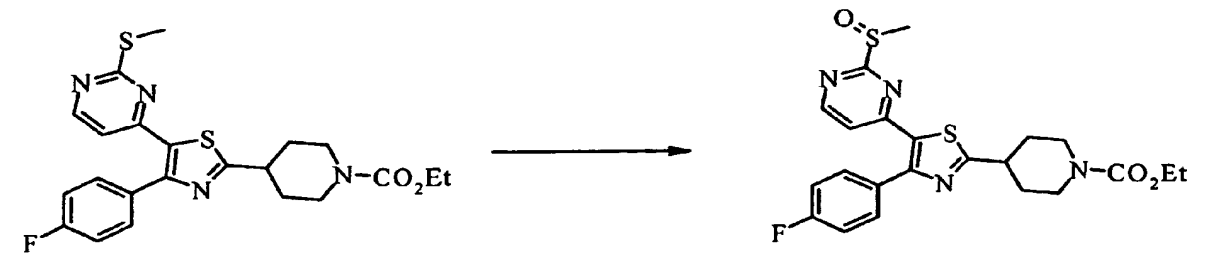
[0019]



$Na_2SO_4$ (6.9g 40mmol) in DMF (100ml) is heated at 120°C for 10min. N-Ethoxycarbonyl-piperidine-4-thiocarboxamide (8.6g 40mmol) is added as a solid and heating continued for 5min. 2-Bromo-2-(2-methylthio-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone (6.8g 20mmol) in DMF (20ml) is rapidly added within 3 seconds and stirring continued at 120°C for 10min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (ethyl acetate/hexanes 5/95 to 10/90) to yield the title compound as yellow crystals (2.2g 24%)
1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 2.58 (s, 3H); 2.91-3.03 (bt, 2H); 3.18-3.28 (m, 1H); 4.20 (q, 2H); 4.25-4.40 (bs, 2H); 6.75 (d, 1H); 7.1 (t, 2H); 7.57 (dd, 2H); 8.31 (d, 1H).
MS (m/z) ESI: 459 (MH+,100).

e) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl-4-pyrimidinyl)thiazole

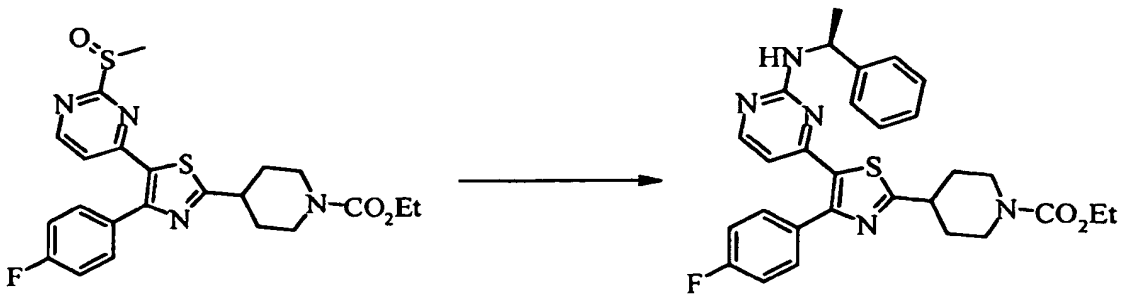
[0020]



4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole (4.0g 8.7mmol) in CH2Cl2 (80ml) is treated with mCPBA (70% 2.1g 8.7mmol) at 0°C for 15min. The reaction mixture is poured on 2N $Na_2CO_3$ and extracted with $CH_2Cl_2$ three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (acetone/hexanes 20/80 to 50/80) to yield the title compound (2.2g 53%) as a white foam.
1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 3.00 (s, 3H); 2.90-3.02 (m, 2H); 3.20-3.30 (bt, 1H); 4.18 (q, 2H); 4.25-4.40 (bs, 2H); 7.15 (d, 1H); 7.20 (t, 2H); 7.56 (dd, 2H); 8.63 (d, 1H).
MS (m/z) ESI: 475 (MH+).

f) 4-(4-Fluoronhenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

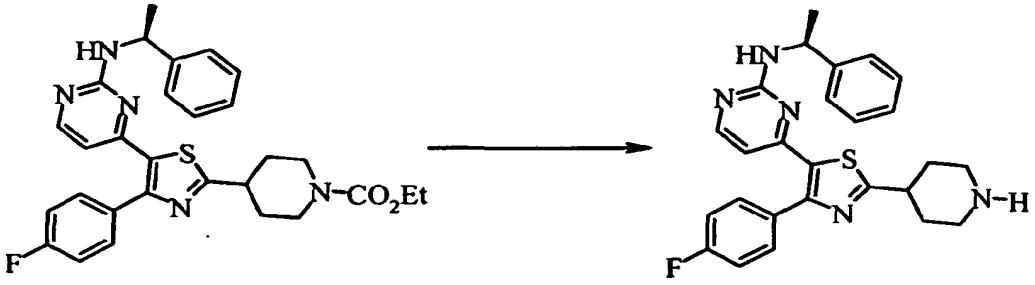
[0021]



4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl-4-pyrimidinyl)thiazole (2.2g 4.6mmol) and 1-(S)-phenylethylamine (2.2ml) are heated at 100°C for 1h. Purification over $SiO_2$ (acetone/cyclohexane 10/90 to 20/80) yielded the title compound as a pale yellow foam (2.4g 95%).
1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.97 (bt, 2H); 3.20 (tt, 1H); 4.20 (q, 2H); 4.30 (bs, 2H); 5.17 (m, 1H); 5.46 (d, 1H, NH); 6.35 (d, l H); 7.12 (t, 2H); 7.30-7.45 (m, 5H); 7.55 (dd, 2H); 8.08 (d, 1H).
MS (m/z) ESI: 523 (MH+, 100).

g) 4-(4-Fluorophenyl-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole

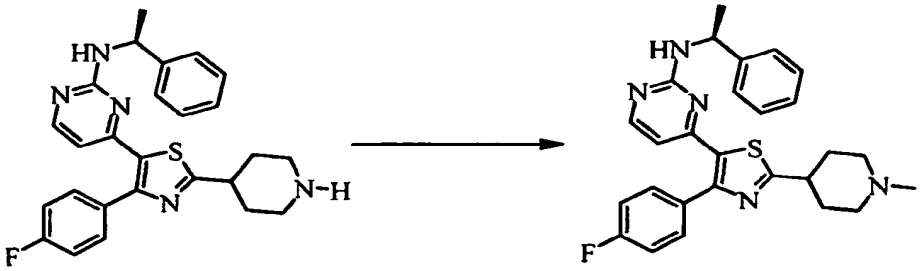
[0022]



4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole (2.4g 4.5mmol) was dissolved in $CHCl_3$ (45ml) and treated with $Me_3SiI$ (1.8ml 13.5mmol) at 60°C for 6h. The reaction mixture was combined with 6M HCl in propanol (18.5m), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice with $CH_2Cl_2$. The combined organic phases were dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (tert.butyl methyl ether /MeOH/NH3conc. 95/4.5/0.5 to 80/18/2) to yield the title compound (1.8g 87%) as a white foam.
1H-NMR (400MHz; $CDCl_3$): 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.82 (dt, 2H); 3.18 (tt, 1H); 3.25 (d, 2H); 5.17 (m, 1H); 5.45 (d, 1H, NH); 6.32 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.07 (d, 1H).
MS (m/z) ESI: 460 (MH+, 100).

## Example 2; 4-(4-Fluorophenyl-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole

[0023]

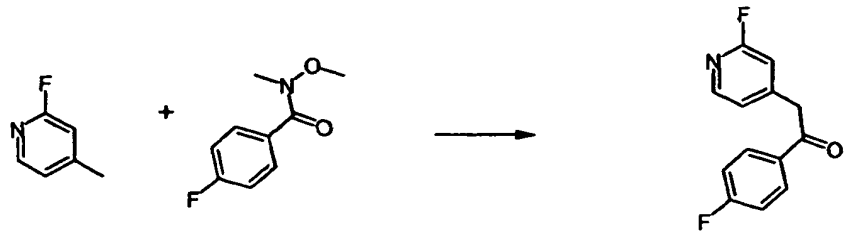


4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole (575mg 1.25mmol) is dissolved in MeOH (12ml) and treated with an aqueous 36%-solution of formaldehyde (0.2ml 2.5mmol) and $NaBH_4$ (95mg 2.5mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (tert.butyl methyl ether /MeOH / $NH_3$conc. 95/4.5/0.5 to 90/9/1) to yield the title compound (600mg 85%) as pale yellow foam.
1H-NMR (400MHz; $CDCl_3$): 1.51 (d, 3H); 1.88-2.01 (m, 2H); 2.08-2.25 (m, 4H); 2.48 (s, 3H); 2.97-3.08 (m, 3H); 5.18 (m, 1H); 5.48 (d, 1H, NH); 6.33 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.05 (d, 1H).
MS (m/z) ESI: 474 (MH+, 100).

## Example 3 4-(4-Fluorophenyl)-2-(piperidin-4-yl).5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

### a) 4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone

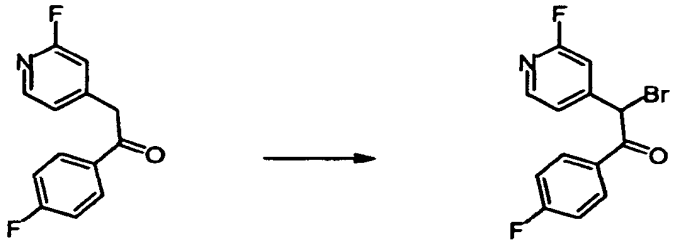
[0024]



Diisopropylamine (0.93 ml; 6.55 mmol) in THF (6 ml) is cooled to -78 C and treated with nBuLi (3.8 ml; 6.08 mmol of a 1.6 M solution in hexane). 2-Fluoro-4-methylpyridine (620 mg; 5.4 mmol) is added dropwise and stirred under argon for 30 min. 4-Fluoro-N-methoxy-N-methylbenzamide (1 g; 5.46 mmol) is added dropwise in THF (0.5 ml) and the reaction mixture allowed to warm up to room temperature within 10 min. then poured on a saturated solution of NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over $Na_2SO_4$, filtered and evaporated to dryness to yield the title compound as pale yellow crystals. Purification by recrystallisation from hot TBME rendered the desired compound as white solid (630 mg; 50 %).
1H-NMR (200 MHz; $CDCl_3$): 4.35 (s, 2H); 6.88 (s, 1H); 7.08-7.30 (m, 3H); 7.99-8.15 (dd, 2H); 8.20 (d, 1H).
MS (e/z) ESI: 233 (M+, 5); 123 (100).

**b) 4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone**

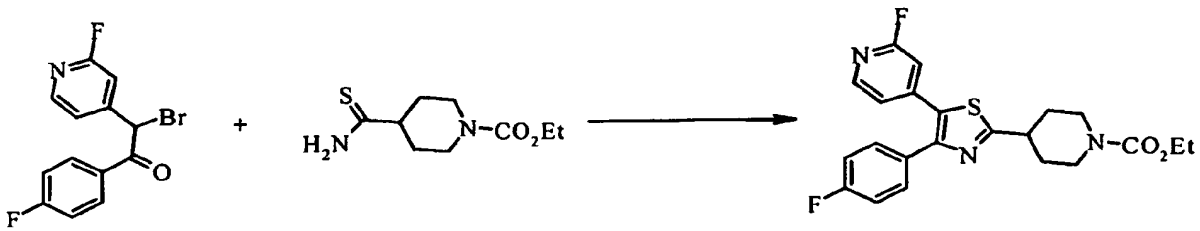
**[0025]**



4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone (0.5 g; 2.1 mmol) dissolved in acetic acid (4 ml) is treated with bromine (0.34 g; 2.1 mmol) in acetic acid (1 ml) at room temperature for 2.5 h under stirring. The light brown solution is evaporated to dryness, dissolved in ether and extracted three times with diethyl ether.The combined organic phases are washed with a saturated solution of $NaHCO_3$, dried over $Na_2SO_4$, filtered and evaporated to dryness to yield the title compound as pale yellow oil (0.67 g; 100%).
1H-NMR (200 MHz; $CDCl_3$): 6.15 (s, 1H); 7.10-7.38 (m, 4H); 8.08 (dd, 2H); 8.23 (d, 1H).
MS (e/z) ESI: 232 (M-Br); 204 (10); 203 (12); 123 (100).

**c) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)$_{th}$iazole**

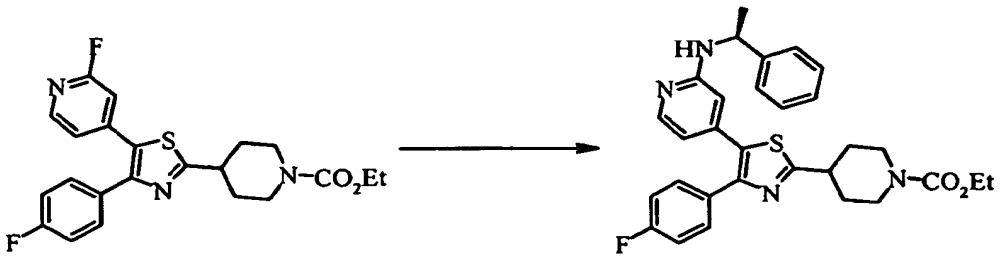
**[0026]**



2-Bromo-2-(2-fluoro-4-pyridyl-(4-fluorophenyl)ethanone (2.5g 8.0mmol) and N-ethoxycarbonyl-piperidine-4-thiocarboxamide (2.1g 9.6mmol) are heated at 60°C in DMF (4ml) for 30min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (ethyl acetate/cyclohexane 20/80 to 100/0) to yield the title compound as an oil (2.5g 70%)
MS (m/z) ESI: 430 (MH+)

d) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

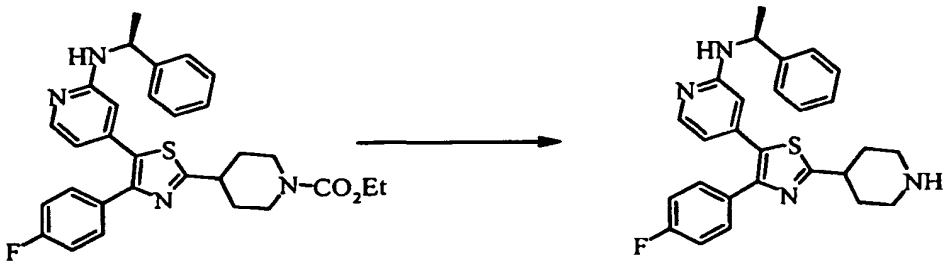
[0027]



4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)thiazole (2.4g 5.5mmol) and 1-(S)-phenylethylamine (5.5ml) are heated to 195°C for 5h. The reaction mixture is evaporated and purified by $SiO_2$ chromatography (ethyl acetate/cyclohexane 20/80 to 30/70) to yield the title compound as a white foam (2.0g 67.3%)
1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.55 (d, 3H); 1.72-1.87 (m, 2H); 2.17 (d, 2H); 2.98 (bt, 2H); 3.15-3.23 (m, 1H); 4.18 (q, 2H); 4.30 (bs, 2H); 4.56 (m, 1H); 5.01 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.95 (dd, 2H); 7.22-7.46 (m, 5H); 7.45 (dd, 2H); 8.03 (d, 1H).
MS (m/z) CI: 531 (MH+, 100).

e) 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

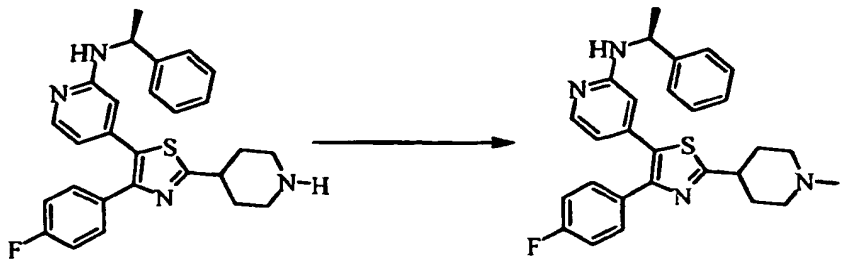
[0028]



4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (2g 3.7mmol) is dissolved in $CHCl_3$ (37ml) and treated with $Me_3SiI$ (1.5ml 11.1mmol) at 60°C for 5h. A second portion of Me3SiI (0.75ml 5.55mmol) was added and stirring continued for another 3h at 60°C. The reaction mixture was combined with 6M HCl in propanol (15ml), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice with $CH_2Cl_2$. The combined organic phases were dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (tert.butyl methyl ether /MeOH / $NH_3$conc. 80/18/2) to yield the title compound (1.2g 71%) as a white foam.
1H-NMR (400MHz; $CDCl_3$): 1.53 (d, 3H); 1.77 (bs, 3H); 2.17 (bd, 2H); 2.78 (bt, 2H); 3.15 (bt, 1H); 3.35 (bd, 2H); 4.55 (m, 1H); 5.00 (d, 1H, NH); 6.17 (s, 1H); 6.50 (d, 1H); 6.97 (bt, 2H); 7.20-7.37 (m, 5H); 7.45 (bt, 2H); 8.02 (d, 1H).
MS (m/z) CI: 459 (MH+)

**Example 4: 4-(4-Fluorophenyl)-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole**

**[0029]**



4-(4-Fluorophenyl)-2-(4-piperidinyl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (500mg 1.09mmol) is dissolved in MeOH (11ml) and treated with an aqueous 36%-solution of formaldehyde (0.17ml 2.18mmol) and $NaBH_4$ (83mg 2.18mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over $Na_2SO_4$, filtered, evaporated to dryness and purified by $SiO_2$ chromatography (tert.butyl methyl ether /MeOH / $NH_3$conc. 95/4.5/0.5) to yield the title compound (550mg 86%) as pale yellow foam.
1H-NMR (400MHz; $CDCl_3$): 1.53 (d, 3H); 1.83-1.98 (m, 2H); 2.07-2.20 (m, 4H); 2.35 (s, 3H); 2.98 (bd, 3H); 4.55 (m, 1H); 4.98 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.98 (t, 2H); 7.22-7.35 (m, 5H); 7.45 (dd, 2H); 8.02 (d, 1H).
MS (m/z) ESI: 473 (MH+)

**[0030]** The Agents of the Invention, as defined above, particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

**[0031]** In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF-α and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

**p38 MAP kinase Assay**

**[0032]** The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in E. coli) is coated onto the wells of microtiter plates (50 µl/well; 1 µg/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 µl aliquots to a final reaction volume of 50 µl.

1. Agents of the Invention titrated from 10 to 0.001 µM in 10-fold dilutions or solvent (DMSO) or $H_2O$.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β-glycerophosphate (Sigma #G-6251):125 mM $MgCl_2$ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.
3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in E. coli)
4. cold ATP (final concentration 120 µM; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 µl/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.

2. Biotin labelled goat-anti-rabbit IgG (50 µl/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 µl/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084) for 30 min at RT.
4. Substrate (100 µl/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + $MgCl_2.6H_20$ (100 mg/l; Merck #5833) + Na Azide (0.2 g/l + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The background value (without ATP) is subtracted and $IC_{50}$ values are calculated using the Origin computer program (4 parameter logistic function).

**[0033]** Agents of the Invention typically have $IC_{50}$S for p38 MAP kinase inhibition in the range from about 100 nM to about 5 nM or less when tested in the above assay.

Assay for Inhibition of TNF-α release from hPBMCs

**[0034]** Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145 : 105. and used at a concentration of $10^5$ cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFNg (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF-α in the supernatant is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Ivention typically suppress TNF release in this assay with an $IC_{50}$ of from about ? nM to about ? nM or less when tested in this assay.

Assay for Inhibition of TNF-α Production in LPS stimulated mice

**[0035]** Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF-α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

**[0036]** LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF-α. Using 20 mg/kg of LPS levels of up to 15 ng of TNF-α / ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

**[0037]** Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

**[0038]** As indicated in the above assays Agents of the Invention are potent inhibitors of TNF-α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

**[0039]** Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNFα and IL-1, e.g., inflammatory conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

**[0040]** Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

**[0041]** Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

**[0042]** Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNFα, e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe bums; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS -related cachexia, e.g., associated with or consequential to HIV infection.

**[0043]** Agents of the Invention are also useful for the treatment of neurodegenerative diseases, such as Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligiodendrocyte loss in multiple sclerosis and inflammatory nervous system diseases, such as neuroinflammatory and stroke.

**[0044]** Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

**[0045]** For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of an Agent of the Invention administered orally once or, more suitably, in divided dosages two to four times/day.

**[0046]** The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg of Agent of the Invention per unit dosage.

**[0047]** In accordance with the foregoing the present invention also provides in a further series of embodiments:

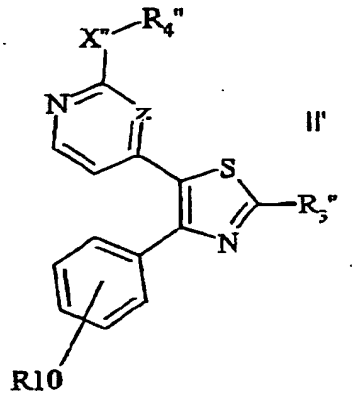
B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an antoimmune or inflammatory disease or condition.

C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.

## Claims

1. A compound of formula II'




wherein

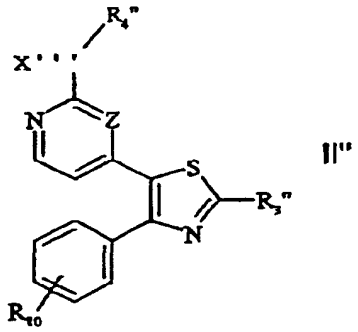
$R_4$" is phenyl or $C_3$-$C_7$cycloalkyl each of which is optionally mono-substituted by halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, hydroxy, trihalomethyl or optionally mono-or di-$C_1$-$C_4$alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 zing atoms and optionally containing a further hetero atom selected from O, S or N;
$R_{10}$ is halogen;
$R_3$" is H, $C_1$-$C_4$alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono-or di-$C_{1-4}$alkyl substituted amino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from $C_1$-$C_4$alkyl, halogen, hydroxy, $C_1$-$C_4$alkoxy, or optionally mono-or di-$C_1$-$C_4$alkyl substituted amino;
Z is N or CH and
X" is -NH-Y'-, -O- or -S-, where Y' is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH(CH_3)$- or a direct bond, and prodrug ester derivatives thereof which are convertible by solvolysis or cleavage under physiological conditions to the compound of formula II' comprising the free hydroxyl group; and acid addition salts thereof.

**2.** A compound according to claim 1 selected from:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methyl-piperidine-1-yl)thiazole;
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidmyl)-2-(4-NH-piperidine-1-yl)thiazole;
4-(4-Fluorophenyl)2-(4-methylpiperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-pyridinyl)thiazole and
4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole;

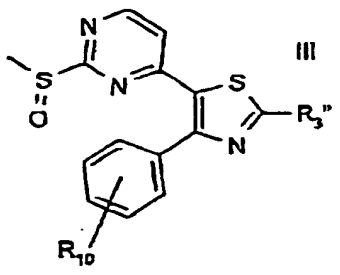
and prodrug ester derivatives thereof which are convertible by solvolysis or cleavage under physiological conditions to the compound of formula II' comprising the free hydroxyl group; and acid addition salts thereof.

**3.** A process for the preparation of a compound of formula II"

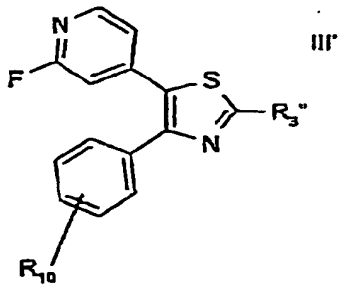



II"

wherein $R_3$", $R_4$", $R_{10}$ and Z are as defined in claim 1 and X"' is NH-, which comprises reacting the corresponding precursor compound of formula m or III'




III




III'

with the corresponding $R_4$"-$NH_2$ amine, wherein $R_3$", $R_4$" and $R_{10}$ are as defined in claim 1, and thereafter, if desired, converting the compound of formula II" obtained into a further compound of formula II" or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

**4.** A compound according to claim 1 or claim 2 for use as a pharmaceutical.

5. A compound according to claim 4 for use in the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

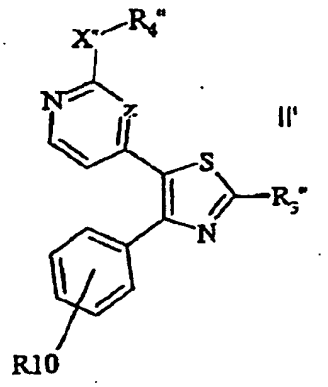
6. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier.

7. A composition according to claim 6 for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

8. Use ofa compound according to claim 1 in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

**Patentansprüche**

1. Verbindung der Formel II'




II'

worin
$R_4$" für Phenyl oder $C_3$-$C_7$ Cycloalkyl steht, das jeweils optional monosubstituiert ist mit Halogen, $C_1$-$C_4$ Alkyl, $C_1$-$C_4$ Alkoxy, Hydroxy, Trihalogenmethyl oder optional mono- oder di-$C_1$-$C_4$ Alkyl-substituiertern Amino oder durch N-Heterocyclyl, das 5 bis 7 Ringatome enthält und optional ein weiteres Heteroatom enthält, das aus O, S oder N ausgewählt ist,
$R_{10}$ für Halogen steht,
$R_3$" für H, $C_1$-$C_4$ Alkyl, Phenyl, Pyridyl, Morpholinyl, Piperidyl, Piperazyl oder optional mono- oder di-$C_1$-$C_4$ Alkyl-substituiertes Amino steht, das jeweils optional beispielsweise mit bis zu 2 Substituenten substituiert ist, die getrennt aus $C_1$-$C_4$ Alkyl, Halogen, Hydroxy, $C_1$-$C_4$ Alkoxy oder optional mono- oder di-$C_1$-$C_4$ Alkyl-substituiertem Amino ausgewählt sind,
Z für N oder CH steht und
X" für NH-Y'-, -O- oder -S- steht, worin Y' für -$CH_2$-, -$CH_2$-$CH_2$-, -$CH(CH_3)$- oder eine direkte Bindung steht
und Prodrugesterderivate hiervon, die durch Solvolyse oder Spaltung unter physiologischen Bedingungen in die Verbindung der Formel II' umwandelbar sind und die freie Hydroxylgruppe umfassen und Säureadditionsalze hiervon.

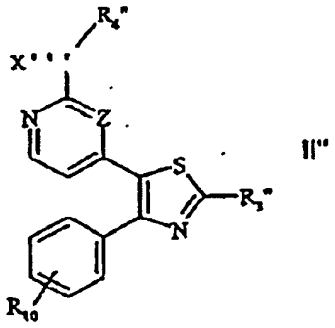
2. Verbindung nach Anspruch 1, die ausgewählt ist aus:

4-(4-Fluorphenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methylpiperidin-1-yl)thiazol,
4-(4-Fluorphenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-NH-piperidin-1-yl)thiazol,
4-(4-Fluorphenyl)-(2-(4-methylpiperidin-1-yl)-5-(2-[cyclopropylmethyl]amino-4-pyridinyl)thiazol und,
4-(4-Fluorphenyl)-2-(4-NH-piperidin-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazol,

und Prodrugesterderivaten hiervon, die durch Solvolyse oder Spaltung unter physiologischen Bedingungen in die

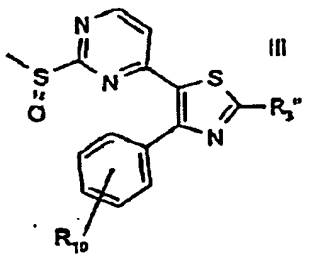
Verbindung der Formel II' umwandelbar sind und die freie Hydroxylgruppe umfassen, und Säureadditionssalzen hiervon.

3. Verfahren zur Herstellung einer Verbindung der Formel II"

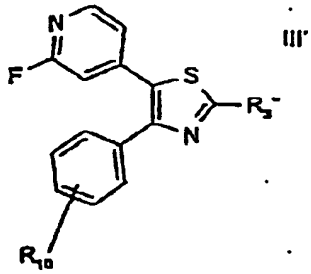


II"

worin $R_3$", $R_4$", $R_{10}$ und Z wie in Anspruch 1 definiert sind und X"' für -NH- steht, durch Umsetzung der entsprechenden Vorläuferverbindung der Formel III oder III'



III



III'

mit dem entsprechenden $R_4$"-$NH_2$ Amin umfasst, worin $R_3$", $R_4$" und $R_{10}$ wie in Anspruch 1 definiert sind und, falls erwünscht, anschließende Umwandlung der erhaltenen Verbindung der Formel II' in eine andere Verbindung der Formel II' oder einen pharmazeutisch annehmbaren und spaltbaren Ester hiervon oder ein Säureadditionssalz hiervon.

4. Verbindung nach Anspruch 1 oder Anspruch 2 zur Verwendung als Pharmazeutikum.

5. Verbindung nach Anspruch 4 zur Verwendung bei der Prävention, Linderung oder Behandlung einer autoimmunen oder inflammatorischen Erkrankung oder eines solchen Zustands.

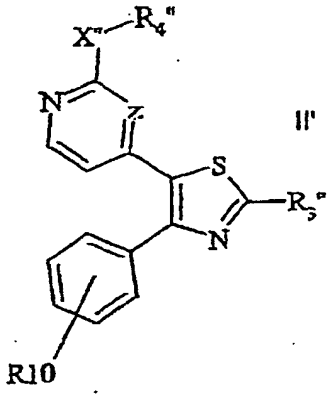
6. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 in Assoziation mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger enthält.

7. Zusammensetzung nach Anspruch 6 zur Verwendung als immunsuppressives oder antiinflammatorisches Mittel oder zur Verwendung bei der Prävention, Linderung oder Behandlung einer autoimmunen oder inflammatorischen Erkrankung oder eines solchen Zustands.

8. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels zur Verwendung als immunsuppressives oder antiinflammatorisches Mittel zur Verwendung bei der Prävention, Linderung oder Behandlung einer autoimmunen oder inflammatorischen Erkrankung oder eines solchen Zustands.

## Revendications

1. Composé de formule II'



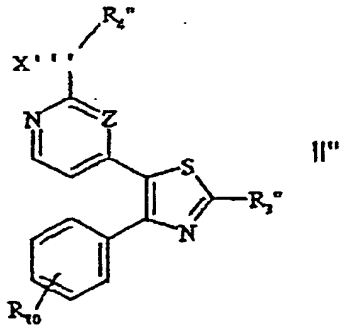
dans laquelle,
$R_4$" est phényle ou $C_3$-$C_7$cycloalkyle chacun étant éventuellement mono-substitué par halogène, $C_1$-$C_4$alkyle, $C_1$-$C_4$alcoxy, hydroxy, trihalométhyle ou, éventuellement, amino mono- ou di-substitué par $C_1$-$C_4$alkyle, ou par N-hétérocyclyle contenant de 5 à 7 atomes cycliques et contenant éventuellement un autre hétéroatome sélectionné à partir de O, S ou N ;
$R_{10}$ est halogène ;
$R_3$" est H, $C_1$-$C_4$alkyle, phényle, pyridyle, morpholinyle, pipéridyle, pipérazyle, ou, éventuellement, amino mono- ou di-substitué par $C_1$-$C_4$alkyle, chacun étant éventuellement substitué par, p.ex., jusqu'à 2 substituants, sélectionnés séparément à partir de $C_1$-$C_4$alkyle, halogène, hydroxy, $C_1$-$C_4$alcoxy, ou, éventuellement, amino mono- ou di substitué par $C_1$-$C_4$alkyle ;
Z est N ou CH et
X" est -NH-Y'-, -O- ou -S-, dans lequel Y' est -$CH_2$-, -$CH_2$-$CH_2$-, -$CH(CH_3)$- ou une liaison directe,
et des dérivés ester d'un promédicament qui peuvent être transformés par solvolyse ou clivage, sous certaines conditions physiologiques, en le composé de formule II' comprenant le groupe hydroxyle libre ;
et un de leurs sels d'addition d'acide.

2. Composé selon la revendication 1 sélectionné à partir de

4-(4-fluorophényl)-5-(2-[1-(S)-phényléthyl]amino-4-pyrimidinyl)-2-(4-méthyl-pipéridine-1-yl)thiazole ;
4-(4-fluorophényl)-5-(2-[1-(S)-phényléthyl1]amino-4-pyrimidinyl)-2-(4-NH-pipéridine-1-yl)thiazole ;
4-(4-fluorophényl)-2-(4-méthylpipéridine-1-yl)-5-(2-[cyclopropylméthyl]amino-4-pyridinyl)thiazole, et
4-(4-fluorophényl)-2-(4-NH-pipéridine-1-yl)-5-(2-(1-(S)-phényléthyl)amino-4-pyridinyl)thiazole ;

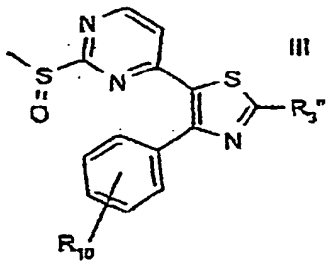
et un de leurs dérivés ester d'un promédicament qui peut être transformé par solvolyse ou clivage, sous certaines conditions physiologiques, en le composé de formule II' comprenant le groupe hydroxyle libre ;
et un de leurs sels d'addition d'acide.

3. Procédé de préparation d'un composé de formule II"

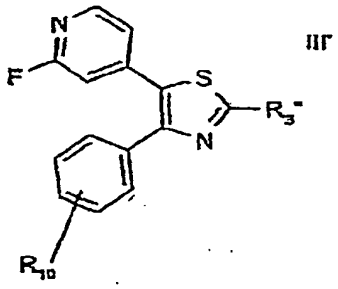


II"

dans laquelle $R_3$", $R_4$", $R_{10}$ et Z sont tels que définis à la revendication 1 et dans laquelle X"' est -NH-, consistant à faire réagir le composé précurseur correspondant de formule III ou III'



III



III'

avec l'amine $R_4$"-$NH_2$ correspondante, dans laquelle $R_3$", $R_4$" et $R_{10}$ sont tels que définis à la revendication 1 et, par la suite, si nécessaire, en convertissant le composé de formule II" obtenu en un autre composé de formule II" ou en un de ses esters pharmaceutiquement acceptables et clivables ou en un sel d'addition d'acide.

4. Composé selon la revendication 1 ou 2 utilisable en tant que produit pharmaceutique.

5. Composé selon la revendication 4 utilisable pour la prévention, l'amélioration ou le traitement d'une maladie ou d'un état autoimmun ou inflammatoire.

6. Composition pharmaceutique comprenant un composé selon la revendication 1 de pair avec un diluant ou véhicule pharmaceutiquement acceptable.

7. Composition selon la revendication 6 utilisable en tant qu'agent immunosuppresseur ou anti-inflammatoire ou utilisable pour la prévention, l'amélioration ou le traitement d'une maladie ou d'un état autoimmun ou inflammatoire.

8. Utilisation d'un composé selon la revendication 1 dans la fabrication d'un médicament utilisable en tant qu'agent immunosuppresseur ou anti-inflammatoire ou utilisable pour la prévention, l'amélioration ou le traitement d'une maladie ou d'un état autoimmun ou inflammatoire.